CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020103, S015

MEDICAL REVIEW(S)

Gallo-Torres

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
MEDICAL TEAM LEADER'S REVIEW

NDA:	20-103/015, SE-1
Sponsor:	Glaxo Wellcome Research Triangle Park, NC
	FEB 1 9 1999
Date Submitted:	August 27, 1998
Drug:	ZOFRAN® (ondansetron hydrocloride) 24 mg tablet strength
Pharmacological Category:	Antiemetic; 5-HT_3-receptor antagonist
Route of Administration:	Oral
Proposed Indication:	Prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy, including cisplatin
Material Reviewed:	The complete supplemental application consists of 18 volumes, including two adequate and well-controlled primary efficacy studies (S3AA3012, S3AA3004/3007), a supporting trial (S3AB3008) and a clinical bioequivalence study (S3AA1002).
Reviewer:	Hugo E. Gallo-Torres, M.D., Ph.D.

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BACKGROUND/INTRODUCTION

Ondansetron (ZOFRAN®) is a selective 5-HT_3 receptor antagonist with well-established anti-emetic activity. Ondansetron is approved for the management of chemotherapy-induced emesis and radiotherapy-induced emesis in the U.S. and more than 80 countries. It is also approved for the prevention and treatment of post-operative-induced nausea and vomiting in the U.S. and more than 30 countries. In the U.S., ondansetron is available as an injection and injecton premixed formulations and as tablets for oral administration.

Currently, ondansetron is approved for the following three indications, at the dosage and administration noted.

1. Prevention of N&V associated with initial and repeat courses of **moderately emetogenic** cancer chemotherapy.

   The recommended adult dosage of ZOFRAN® tablets is **one 8-mg tablet given twice a day.**

2. **Prevention of N&V associated with radiotherapy** in patients receiving either total body irradiation, single high-dose fraction to the abdomen, or daily fractions to the abdomen.

   The recommended oral dose of ZOFRAN® tablets is **one 8-mg tablet given three times a day.**

   [NOTE: This indication is not the subject of the present NDA supplement but this information is included here for completeness purposes.]

3. Prevention of post-operative N&V.

   The recommended oral dosage is 16 mg given as a single dose (two 8-mg tablets 1h before induction of anesthesia).

   [NOTE: This indication is not the subject of the present NDA supplement but this information is included here for completeness purposes.]

In the U.S., ondansetron is available as:

- ZOFRAN® 4-mg tablets (ondansetron hydrochloride dihydrate equivalent to 4 mg of ondansetron base) and
- ZOFRAN® 8-mg tablets (ondansetron hydrochloride dihydrate equivalent to 8 mg of ondansetron base). In addition, approval of a ZOFRAN® ODT oral disintegrating tablet is pending.

The present supplement to NDA 20-103 for ZOFRAN® tablets includes new data in support of the registration of a 24-mg ZOFRAN® tablet strength for the following indication:

Prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy, including cisplatin.

The sponsor notes that ondansetron tablets 24-mg have been developed to provide a single oral dose for the control of emesis in patients receiving highly emetogenic chemotherapy. The proposed market form has been designed as an easily swallowed, film-coated tablet providing size differentiation from ZOFRAN® tablets 4 mg and 8 mg. Based on these new data, revisions are proposed to the following SECTIONS/ Subsections of the currently approved labeling for ZOFRAN® (ondansetron hydrochloride) tablets and ZOFRAN® (ondansetron hydrochloride) Oral Solution. **The bulk of these proposed revisions are related to the 24-mg new dosage form.**

NOTE: The actual wording is not included because, at the end, a recommendation is made not to include most of these proposed revisions. The reviewer's proposed revisions to the labeling are being addressed separately.

- DESCRIPTION [lines 22 and 23; lines 25 and 26]
- CLINICAL PHARMACOLOGY
- Pharmacokinetics [lines 56 through 59]
  [lines 72 through 76]
- CLINICAL TRIALS:
  - Chemotherapy-Induced Nausea and Vomiting:
    Highly Emetogenic chemotherapy:
  [lines 91 through 114].
- Elderly Patients
  [lines 160 to 161].
- INDICATIONS AND USAGE

  [lines 196 to 197]
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- ADVERSE REACTIONS
  Chemotherapy-Induced Nausea and Vomiting
  [lines 250 and 251].
  [lines 254 and 555].
  [lines 256 through 263].

  Postoperative Nausea and Vomiting
  [line 291].

- DOSAGE AND ADMINISTRATION
  [lines 307 through 312].

- HOW SUPPLIED
  [lines 370 through 373]
  [lines 385, 387 to 388].

II. MATERIALS SUBMITTED IN SUPPORT OF THE SPONSOR'S APPLICATION TO REGISTER A 24-mg ZOFRAN® TABLET

In support of the current application to register a 24 mg ZOFRAN® tablet for single-dose administration for the prevention of N&V associated with the administration of highly-emetogenic cancer chemotherapy, including cisplatin, the sponsor has submitted the results of the following four trials:

- a bioequivalence study (S3AA1002)
- 2 adequate and well-controlled primary efficacy studies (S3AA3012 and S3AA3004/3007) and
- a supporting study (S3AB3008).

Preliminary comments on the adequacy of this information in support of the claims are given below under A., B., and C. below.

A. Protocol S3AA1002

"A bioequivalence study comparing three 8 mg ondansetron (ZOFRAN®) tablets to a single 24 mg ondansetron tablet"

[Report RM1997/00392/00; USA; Dr. Moeller]

This randomized, single-dose, open-label, 2 period, crossover study was performed to evaluate the relative bioavailability of ondansetron from three ZOFRAN® 8 mg tablets vs one 24 mg tablet. Sixteen participating healthy subjects (8 M and 8F), ranging in age from 18 to 43y completed both arms of the trial and gave evaluable results. All doses were taken with 200 ml water; there was a 3-7 day washout between consecutive doses. The sampling period was sufficient for accurate estimates of AUC_{α} to be obtained. The primary analysis was performed on log-transformed values. Geometric least square means and 95% confidence intervals (CIs) were calculated for each treatment and geometric least squares means ratios and 90% CIs were calculated to compare the treatments.

- The summary of PK parameters is provided in Table 1.

TABLE 1
Study S3AA1002

IN VIVO STUDY DATA SUMMARY

Dosage Form	Statistic Reported	$AUC_{0-\infty}$ (ng-h/mL)	C_{max} (ng/mL)	T_{max} (h)	$T_{1/2}$ (h)
Oral Tablet 8 mg x 3 [n=16]	Geo. Mean 95% CI	882.9 (831.9, 937.0)	140.2 (130.8, 150.3)	1.50 (1.00 - 6.00)	5.13 (4.62, 5.68)
Oral Tablet 24 mg x 1 [n=16]	Geo. Mean 95% CI	923.8 (870.4, 980.4)	152.5 (142.3, 163.5)	2.00 (1.00 - 2.00)	5.45 (4.92, 6.05)
	Ratio 90% CI	1.05 (0.98, 1.12)	1.09 (1.00, 1.18)	0.00 (-0.50, 0.25)	1.06 (0.94, 1.20)

This Table corresponds to sponsor's Table 3.3 (vol. 1, p. 71), with major modifications

Geometric LS Mean and 95% CI with geometric LS ratio (Test/Reference) and 90% CI for all parameters except T_{max} Median and range with median difference and 90% CI for T_{max}

- Bioequivalence data are summarized in Table 2.

TABLE 2
Study S3AA1002

BIOEQUIVALENCE STUDY RESULTS

Parameter	Treatment	Geometric LS mean	95% CI[a]	Geometric Mean Ratio[b]	90% CI
C_{max} (ng/mL)	24 mg tablet 3x8mg tablets	152.5 140.2	142.3, 163.5 130.8, 150.3	1.09	1.00, 1.18
t_{max} (h)	24mg tablet 3x8mg tablets	2.00 1.50	1.00 - 2.00 1.00 - 6.00	0.00	-0.50, 0.25
AUC_{last} (ng.h/mL)	24mg tablet 3x8mg tablets	878.1 843.0	831.1, 927.8 797.9, 890.7	1.04	0.98, 1.11
AUC_{∞} (ng.h/mL)	24mg tablet 3x8mg tablets	923.8 882.9	870.4, 980.4 831.9, 937.0	1.05	0.98, 1.12
t½ (h)	24mg tablet 3x8mg tablets	5.45 5.13	4.92, 6.05 4.62, 5.68	1.06	0.94, 1.20

This Table corresponds to sponsor's Table 3.4 (vol. 1, p. 72) with minor modifications.

a,b) Geometric LS Mean and 95% CI with geometric LS ratio (Test/Reference) and 90% CI for all parameters except T_{max}. Median and range with median difference and 90% CI for T_{max}.

- The 90% CI for the least squares means ratios for C_{max}, AUC_{last} and AUC_{α} lay within the range for acceptance of bioequivalence between the two treatment arms (0.80 – 1.25). It is therefore concluded that one ondansetron 24 mg tablet and 3 x ZOFRAN® 8 mg tablets are bioequivalent. These two dosage forms may be used interchangeably.[1]

- No serious AEs were reported. A total of 8 AEs were reported in 6/16 subjects. The most fr3equent AE was mild headache which was reported in 6/16 subjects. There were no significant laboratory abnormalities. The 24 mg oral dose of ondansetron was safe and well-tolerated in these healthy volunteers. No new or unexpected AEs were reported.

B. Primary Efficacy Trials

- Table 3 summarizes the main design and execution of the two randomized, double-blind, active-comparator, parallel, multicenter studies. These primary efficacy trials assess the efficacy and safety of a single 24-mg dose for the prevention of highly emetogenic chemotherapy-induced N&V. Also included in this Table, under the column labeled REMARKS are initial comments on the adequacy of these clinical trials (S3AA3012 and S3AA3004/3007) submitted in support of the indication proposed by the sponsor. If found properly executed, these two trials can be considered critical for approval.

C. Supportive Efficacy Trial

As summarized in Table 3, the design of this trial is inadequate and it will not be reviewed. It cannot be considered supportive.

[1] Reproduced below are the sponsor's conclusions from Clinical PK Studies (under review by Biopharm).

- Three Zofran® 8mg Tablets are bioequivalent to and may be used interchangeably with one Ondansetron 24mg Tablet.
- The Zofran® 8mg Tablet is bioequivalent to the clinical trial formulation Ondansetron 8mg Tablet.
- The market image Ondansetron 24mg Tablet is considered equivalent to the clinical trial formulation Ondansetron 24mg Tablet based upon the similarity of the formulations and in-vitro dissolution data. The human pharmacokinetic and bioavailability studies have not revealed any new or unexpected adverse events associated with single oral doses of ondansetron 24mg.

TABLE 3

N&A 20-103, Ref. No. 15, SE1

Study Identification, Main Features of Design, Main Characteristics of the Study Population, Emetogenic Potential and Doses Being Compared in the Two Pivotal and One Supportive Clinical Trials Submitted in Support of the Efficacy and Safety of 24 mg ZOFRAN® Tablets for the Prevention of N&V Associated with Highly Emetogenic Cancer Chemotherapy, Including Cisplatin

Protocol No.	Main Design Features	Study Population	Emetogenic Potential	Group Being Compared	REMARKS
I. PIVOTAL TRIALS					
S3AA3012 (RM1998/00122/00) [n=357] M=68% F=32% 60 Investigators (USA, Puerto Rico and Mexico)	3-arm, randomized, double-blind, multicenter, single oral dose, 24-h study period Escape medication if patient had severe emesis during the 24-h period following cisplatin administration	M or F, at least 12y of age, median age 64y. Pts had a histologically confirmed diagnosis of cancer, with minimum Karnosky performance status of 60%. The site of primary neoplasm that occurred with the highest frequency was the lung, followed by head and neck. Scheduled to receive cisplatin-based regimens for the first time.	**High** • Chemotherapy regimens containing ≥50 mg/m^2 cisplatin administered over a period of ≤3h. Other chemo-therapy agents of low to moderate emetogenicity could also be administered..	The following was administered 30 min. prior to the initiation of cisplatin infusion (1:1:1): ZOFRAN® (po Tablets) • 8 mg BID [n=124] vs • 24 mg QD [n=116] vs • 32 mg QD [n=117]	• Useful design. • At least 116 patients were randomized to each of the 3 arms of the trial. • Cisplatin-based chemotherapeutic regimens were of high emetogenic potential. • Efficacy during the Acute Phase (24 after chemotherapy administration) is demonstrated by showing statistical superiority of the 24-mg dose over the lowest ondansetron dose (8 mg b.i.d.). In this side-by-side comparison, demonstration that the approved intravenous regimen (32 mg QD) for prevention of N&V induced by highly emetogenic regimens, including cisplatin, is also superior to the low dose, would allow for demonstration of efficacy of the oral 24 mg dose level similar to that of the 32 mg dose level. However, the 32 mg of the drug is not being administreed intravenously. Thus, the 32 mg oral OND arm is technically experimental (not approved for any indication). Ideally, the 24 mg OD should also be shown superior to the 32 mg OD but that might be asking too much of the 24 mg dose. Therefore, comparability between these dose levels of the drug may be acceptable to show that the 24 mg OD dose is effective.

S3AA3004/3007 (RM1997/04252/00) [n=373] M=56% F=44% 38 Investigators (USA)	-3004 and -3007 were two identical, 2-arm, randomized, parallel, double-blind comparative, single oral dose, multicenter trials. 24-h study period Escape medication if patient had severe emesis during the 24-h period following cisplatin (or carboplatin) administration.	M or F, ranging in age between 32 and 86y. Pts. had a histologically confirmed diagnosis of cancer, with Karnosky performance status of 60%. The site of primary neoplasm that occurred with the highest frequency was the lung (59%), other types of tumors occurred at lower rates. Scheduled to receive i.v. cisplatin or carboplatin.	**HIGH** • Median dose of cisplatin was 70 mg/m^2 (range=31 to 100 mg/m^2) Median time of infusion was 2h • Concomitant chemotherapies included etoposide, MTX and 5-FU	The following was administered 30 min prior to the initiation of cisplatin or carboplatin infusion (1:1): • ondansetron tablet, 24 mg (po) QD (single dose) [n=184] vs • granisetron, 10 µg/Kg single i.v. infusion [n=187]	• Useful design • At least 184 patients were randomized to each of the 2 arms of the trial. • Cisplatin (or carboplatin)-based chemotherapeutic regimens were of high emetogenic potential • Efficacy during the Acute Phase (24h after chemotherapy administration) is demonstrated by showing bioequivalence between the 24-mg oral ondansetron and the approved i.v. regimen of granisetron (10 µg/Kg).
II. SUPPORTIVE TRIAL					
S3AB3008 (GM1997/00089/00) M=61% F=39% [n=530] 30 non-USA Investigators (Canada, France, Germany, Iceland, Italy, Poland, South Africa, U.K.)	2-arm, randomized, double-blind, double-dummy, parallel group, combination trial. Post-treatment assessment between 24h (Day 1) and 28 days after the start of cisplatin	M or F, mean age=53y. Chemotherapy-naïve pts.	**HIGH(?)** • Although the median cisplatin was 75 mg/m^2, this dose may not have been highly emetogenic because it was infused over a period of ≤4h.	Pts. were randomized (1:1) to one of 2 groups: • **Oral group** oral OND 24 mg plus oral DEX 12 mg and 2 saline (PL) I.V. infusions **vs** • **I.V. group** PL tablets plus PL capsules and DEX 20 mg i.v. plus OND 8 mg i.v.	• Not a useful design. It attempts to answer too many questions, with many variables. • The cisplatin-base regimen may not have been highly emetogenic because it was infused for ≤4h. • The study may be hypothesis generating. It attempts to show bioequivalence between oral OND plus oral DEX and I.V. OND plus a dose of 20 mg I.V. DEX, which is different from the DEX oral dose in the other group. This approach does not allow sound efficacy conclusions to be made. • This trial will not be reviewed.

Reviewer's Table

III. STUDY S3AA3012 (REPORT RM1998/00122/00)

1. Title

"A randomized, double-blind study of oral ondansetron, 8mg twice daily, 24mg once daily and 32mg once daily, in the prevention of nausea and vomiting associated with cisplatin chemotherapy"

NOTE: The description of the Protocol that follows includes two amendments. **Amendment #01** (origination date, 25 June 1996) modified the setting to include Mexico, modified the inclusion criteria to include women of childbearing potential with or without maintained contraception, amended the content of Control Methods to specify that Glaxo Wellcome Inc. Produce Surveillance staff would break the blind for treatment assignment in the event of a Serious Adverse Event (SAE), changed the statistical test to be used for evaluating nausea assessments among the three groups from the Wilcoxon rank sum test to the van Eleteren test, modified the definition of an SAE, and modified the instructions for investigator reporting of an SAE to Glaxo Wellcome, Inc. **Amendment #02** (origination date, 27 March 1997) modified the exclusion criteria to allow subjects to receive selective serotonin re-uptake inhibitors and tricyclic antidepressants during the study period provided the subject had been on stable doses for at least 2 weeks prior to study entry and no increase in dosage occurred during the 24.5-hour study period, updated Glaxo Wellcome, Inc. contact information for reporting an SAE, and updated Appendix 3 to include the most recent version of the package insert.

2. Objectives

1) To evaluate the antiemetic efficacy (as assessed by emetic episodes and nausea scores) of oral ondansetron, 8 mg twice daily, 24 mg once daily, and 32 mg once daily, in the prevention of nausea and vomiting associated with cisplatin ($\geq$50 mg/m^2) chemotherapy.

2) To evaluate the safety profile (as assessed by clinical adverse events and laboratory evaluations) of oral ondansetron, 8 mg twice daily, 24 mg once daily, and 32 mg once daily, in the prevention of nausea and vomiting associated with cisplatin chemotherapy.

3. Study Population (Table 4)

In this Table, the inclusion/exclusion criteria are listed. These criteria were adequate for the proposed objectives of the trial. In the main, the study population consisted of M or F patients (at least 12y of age, median age 64y) who had a histologically confirmed diagnosis of cancer, a Karnosky performance status of 60% or more and who were scheduled to receive cisplatin-based regimens for the first time. The site of primary neoplasm that occurred with the highest frequency was the lung, followed by head and neck.

TABLE 4
Study S3AA3012 (Report RM1998/00122/00)

CHARACTERISTICS OF THE STUDY POPULATION

INCLUSION CRITERIA	REASONS FOR EXCLUSION
• M or F who were surgically sterilized, post-menopausal, or pre-menopausal with a negative pregnancy test • At least 12 y of age • Histologically confirmed diagnosis of cancer • Receiving their first course of cisplatin containing cancer chemotherapy • Scheduled to receive cisplatin $\geq$50 mg/m^2 administered over a period of $\geq$3 h • Signed an IC, or if the subject was <18 y of age, had a legal guardian sign an IC • Able to read and write at a competent level to allow for adequate completion of the diary APPEARS THIS WAY ON ORIGINAL	• Karnofsky performance status <60% • Received an investigational drug in the previous 30 days or were scheduled to receive any investigational drug during the study period • Experienced nausea and/or vomiting while receiving non-cisplatin cancer chemotherapy during the previous six months • Chronic nausea and/or vomiting due to other etiologies, including but not limited to gastric outlet obstruction, increased intracranial pressure, or brain metastases • Experienced retching or vomiting or uncontrolled nausea within 24 h prior to administration of test medication • Received medication with known or potential antiemetic/serotonergic activity within the 24-h period prior to receiving test medication. Among these compounds are phenothiazines, butyrophenones, hydroxyzine, lorazepam, cannabinoids, MCP, corticosteroids (topical steroids for skin disorders and inhaled steroids for respiratory disorders were allowed), trimethobenzamide, monoamine oxidase inhibitors, lithium, serotonin re-uptake inhibitors (e.g., fluoxetine) and 5-HT$_3$ antagonists. Subjects who might require one or more of these medications during the 24.5-h tereatment period were also excluded. Benzodiazepines other than lorazepam were allowed within 24 h prior to and during the study period, but only when used for indications such as anxiety or to induce sleep. [NOTE: Amendment 02 allowed subjects to receive selective serotonin re-uptake inhibitors and tricyclic antidepressants during the study period provided the subject had been on stable doses for at least 2 weeks prior to study entry and no increase in dosage occurred during the 24.5-h study period.] • Received radiation therapy involving the abdomen or the pelvis within 48 h prior to or were scheduled to receive such radiation during the 24.5-h treatment period • Scheduled to receive cyclophosphamide $\geq$500 mg/m^2, nitrogen mustard(s), DTIC, procarbazine, carmustine, ifosfamide, carboplatin, or an additional dose of cisplatin during the study period • Any current or past medical condition(s) (e.g., vagotomy) and/or required medication to treat a condition(s) that could confound the evaluation of the data collected in this clinical trial • Had a contraindication to receiving ondansetron as indicated on the Zofran® package insert

Reviewer's Table

Abbreviations:
M=males; F=females; DTIC=dacarbazide, IC=Informed consent; MCP=metoclopramide.

4. Study Design

From the review of the evidence, the study was double-blind, parallel, randomized, multicenter and comparative, consisting of three arms. The use of corticosteroids (such as dexamethasone= DEX) was not allowed as the intent was to demonstrate the activity of OND alone.

- Baseline assessments of nausea were obtained within the 30 min. before test medication administration. Throughout the 24.5-h study period subjects were requested to document the occurrence of emesis.

- At the end of the 24-h study period or immediately prior to withdrawal, assessments of nausea were obtained. Blood samples for laboratory safety studies were obtained within eight days or less following test medication administration for laboratory safety studies.

- Control Group

In the absence of a placebo-controlled group, the FDA-approved dosage regimen of oral OND 8 mg BID served as a control group.

It is worth noting that OND 8 mg BID is only aproved for use with moderately emetogenic chemotherapy. According to a publication by Beck et al.[2] the Complete Response (CR) rate, defined as no emesis over the 3-day study period, for oral OND 8 mg BID in subjects receiving moderately emetogenic chemotherapy (cyclophosphamide-based chemotherapy containing either MTX or doxorubicin) was 61%.

5. Randomization/Blinding/Anti-Emetic Treatment

These aspects of the trial were adequate.

- Subjects were randomized (1:1:1 ratio) within blocks of six to receive one of the three treatment arms: 8 mg BID, 24 mg QD or 32 mg QD. One randomization schedule[3] was used for all investigators.

- The randomization schedule was provided in sponsor's Appendix 3 and a subject listing of treatment allocation was provided in sponsor's Appendix 5. Their Table 23 listed the disposition of treatment numbers allocated per investigational site.

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[2] T.M. Beck et al. Oral ondansetron 8 mg twice daily is as effective as 8 mg three times daily in the prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy. Cancer Investigation 15:297-303 (1997)].

[3] Each investigator was sent a sequential set of 12 randomization numbers and corresponding test medication supplies. The randomization schedule was generated by the Medical Data Sciences Department at Glaxo Wellcome Inc. As subjects were identified for participation in the study, the principal investigator's designee (pharmacist or research nurse) assigned the next consecutive treatment number according to the drug dispensing log prepared at Glaxo Wellcome, Inc. for his/her site.

- Adequate methods for double-blinding were used. Blinding was achieved as follows.

Treatment Arm	n	Ondansetron		
		Dose 1		Dose 2
		White Tablet	Pink Tablet	White Tablet
I. 8 mg BID	107	8 mg	placebo	8 mg
II. 24 mg QD	107	placebo	24 mg	placebo
III. 32 mg QD	107	8 mg	24 mg	placebo

- **Anti-emetic Treatment/Materials Specifications**[4]

All subjects were dispensed three bottles of blinded study drug containing the following:

Bottle A: (Dose 1) White Tablet
Bottle B: (Dose 1) Pink Tablet
Bottle C: (Dose 2) White Tablet

All subjects were to have the first dose of study drug administered by a research staff member 30 min. prior to the initiation of cisplatin. The second dose of study drug (white tablet) was to be taken 8 h from the time the first dose was ingested. Prior to leaving the treatment facility, outpatients were instructed by study personnel regarding when Dose 2 should be taken. Inpatients were administered Dose 2 either by research personnel or by the unit nursing staff.

- Labeling/Drug Accountability [redacted] APPEARS THIS WAY ON ORIGINAL

These aspects of the trial were adequate.

6. Emetogenic Stimulus (Chemotherapy Treatment)

Beginning 30 min. after administration of Dose 1 of study drug, cisplatin was administered as a short intravenous infusion (≤3 h) at a dose of ≥50 mg/m^2. Other chemotherapy agents of low to moderate emetogenicity could also be administered during the 24-h study period.

[4] Study materials from the following batches were supplied by Glaxo Wellcome, Inc. for use in this study.

Drug Name	Strength	Batch Number	Expiration/review date
Ondansetron	24 mg tab	6ZM0133	30-Apr-2000
Ondansetron	24 mg tab	A93B85	30-Nov-1998
Ondansetron	PL tab	A94B64	31-May-1998
Ondansetron	PL tab	F93/169A	31-Jul-1998
Ondansetron	8 mg tab	F95/076B	30-Jun-1998
Ondansetron	PL tab	F96/088B	31-Aug-2000
Supplies were shipped to investigational sites between 10 July 1996 and 16 February 1998.			